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NUTTER MCCLENNEN & FISH LLP
WORLD TRADE CENTER WEST
155 SEAPORT BOULEVARD
BOSTON, MA 02210-2604

EXAMINER	
CARTER, KENDRA D	
ART UNIT	**PAPER NUMBER**
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	. 10/728,056	ZERVOS, ANTONIS	
	Examiner	Art Unit	
	Kendra D. Carter	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 32-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14,20-22, and 28-31* is/are rejected.

7)☒ Claim(s) *13,15-19 and 23-27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-11, are drawn to a pharmaceutical composition for inhibiting cellular apoptosis comprising at least one apoptosis inhibiting compound that can modulate caspase-independent apoptosis, classified in class 424, subclass 9.2 and 158.1 for example.

II. Claims 12-31, are drawn to a method for inhibiting caspase-independent apoptosis in a cell, inhibiting Omi/HtrA2 activity, and modifying a disorder associated with caspase-independent apoptosis, classified in class, 514 subclasses 256 and 879 for example.

III. Claims 32-40, are drawn to a method of preventing tubular cell death, classified in class 514, subclass 256 and 869 for example.

IV. Claims 41-53, are drawn to a method for identifying a substrate associated with caspase-independent apoptosis and identifying a compound that inhibits caspase-independent apoptosis, classified in class 436, subclass 503 for example.

The inventions are distinct, each from the other because of the following reasons:

Inventions of Group I and Group II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the composition of Group I can be used to prevent tubular cell death.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art in view of their different classification, restriction for examination purposes as indicated is proper.

Inventions of Group I and Group III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the composition of Group I can be used to modifying a disorder associated with caspase-independent apoptosis.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art in view of their different classification, restriction for examination purposes as indicated is proper.

Inventions of Group I and Group IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the composition of Group I can be used to modifying a disorder associated with caspase-independent apoptosis.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art in view of their different classification, restriction for examination purposes as indicated is proper.

Inventions of Group II and Group III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In

the instant case, the different inventions do not have the same mode of operation. The method of group III does not have to occur through a caspase-independent pathway.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

Inventions of Group II and Group IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions do not have the same effect. The method of group II already has a compound to administer, whereas the method of group IV is looking for a compound.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

Inventions of Group III and Group IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have

different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions do not have the same mode of operation or the same effect. First, the method of group III does not have to occur through a caspase-independent pathway. Second, the method of group II already has a compound to administer, whereas the method of group IV is looking for a compound.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the

requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

During a telephone conversation with George Xixis on March 3, 2007 a provisional election was made with traverse to prosecute the invention of Group II, claims 12-31. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-11 and 32-53 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Objections

(1) Claims 15-19 and 23-27 are objected to because the structure or the proper name of the compounds should be included in the claim versus referring to the Figure number. Appropriate correction is required.

(2) Claim 13 is objected to because the word "contracting" should be contacting. Appropriate correction is required.

(3) Claims 15-19 and 23-27 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(1) Claims 12-15, and 17-19, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting caspase-independent apoptosis in a cell comprising the compound ucf-101 (i.e. Fig 1b; see specification page 45, example 15), does not reasonably provide enablement for all apoptosis inhibiting compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to using the invention commensurate in scope with these claims.

The instant claims are drawn to a method of inhibiting caspase-independent apoptosis in a cell comprising contacting a cell having Omi/HtrA2 activity with at least one apoptosis inhibiting compound. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the invention:

The claim 12 is drawn to "a method for inhibiting caspase-independent apoptosis in a cell comprising contacting a cell having Omi/HtrA2 activity with at least one apoptosis inhibiting compound, such that the apoptosis inhibiting compound interacts with Omi/HtrA2 to inhibit the activity of Omi/HtrA2, wherein the inhibition of Omi/HtrA2 activity reduces apoptosis in the cell; and monitoring the inhibition of apoptosis." The claim 15 is drawn to "a method of claim 12, wherein the apoptosis inhibiting compound is selected from the group consisting of the structure shown in Fig. 1a, Fig. 2a, Fig. 3a

and Fig. 4a." The claim 17 is drawn to "a method of claim 12, wherein the apoptosis inhibiting compound is the structure shown in Fig. 2b. The claim 18 is drawn to "a method of claim 12, wherein the apoptosis inhibiting compound is the structure shown in Fig. 3b. The claim 19 is drawn to "a method of claim 12, wherein the apoptosis inhibiting compound is the structure shown in Fig. 4b.

(2) The breadth of the claims:

Claims 12-14 embraces inhibiting caspase-independent apoptosis comprising contacting a cell having Omi/HtrA2 activity with an apoptosis inhibiting compound. This reads on inhibiting caspase-independent apoptosis, with any apoptosis inhibiting compound. The specification does not enable inhibition caspase-independent apoptosis with any apoptosis inhibiting compound. Claims 15, 17-19 embraces inhibiting caspase-independent apoptosis comprising: contacting a cell having Omi/HtrA2 activity with the apoptosis inhibiting compound is selected from the group consisting of the structure shown in Fig. 1a, 2a, 2b, 3a, 3b, 4a, and 4b. This reads on inhibiting caspase-independent apoptosis, with the above compounds. The specification does not enable inhibition of caspase-independent apoptosis with the above compounds.

(3) The state of the prior art:

The state of the art regarding inhibition of caspase-independent apoptosis with any apoptosis inhibiting compound, more specifically with the structure shown in Fig. 1a, 2a, 2b, 3a, 3b, 4a, and 4b is very low or do not exist.

(4) The predictability or unpredictability of the art:

The predictability of inhibiting caspase-independent apoptosis with any apoptosis inhibiting compound, more specifically with the structure shown in Fig. 1a, 2a, 2b, 3a, 3b, 4a, and 4b is relatively low. Therefore, to one skilled in the art, inhibiting caspase-independent apoptosis with any apoptosis inhibiting compound, more specifically with the structure shown in Fig. 1a, 2a, 2b, 3a, 3b, 4a, and 4b is highly unpredictable.

(5) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented / working examples:

In the instant case, the guidance of the specification as to the inhibition of caspase-independent apoptosis with any apoptosis inhibiting compound, more specifically with the structure shown in Fig. 1a, 2a, 2b, 3a, 3b, 4a, and 4b is completely lacking. The specification as filed does not speak on or show any working examples any studies performed that inhibit caspase-independent apoptosis with any apoptosis inhibiting compound. The specification does show on page 45 and 46 the structure shown in Fig. 1b (Ucf-101) protects MPT cells from cisplatin-induced apoptosis (see

page 46, paragraph 2, lines 14-16). Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2194.

(7) The quantity of experimentation necessary:

The instant claims read on inhibiting caspase-independent apoptosis with any apoptosis inhibiting compound, more specifically with the structure shown in Fig. 1a, 2a, 2b, 3a, 3b, 4a, and 4b. As discussed above the specification fails to provide any support for inhibiting caspase-independent apoptosis with any apoptosis inhibiting compound, more specifically with the structure shown in Fig. 1a, 2a, 2b, 3a, 3b, 4a, and 4b. Applicant fails to provide any information sufficient to practice the claimed invention, absent undue experimentation. As stated above, the compound with the structure shown in Fig. 1b (ucf-101) protects MPT cells from cisplatin-induced apoptosis (see page 46, paragraph 2, lines 14-16). Although the specification teaches that the compounds shown in Fig. 1a, 2a, 2b, 3a, 3b, 4a, and 4b show significant and specific activity against Omi/HtrA2 in an in vitro assay (see page 19, lines 9-11), this does not give support that the same compounds will inhibit caspase-independent apoptosis for the following reasons: (1) the compound shown in Fig. 1b (ucf-101) has the highest activity against Omi/HtrA2 (see specification page 19, lines 10-11 and page 37, lines 18-19 and 22-24), which means it is the most potent compound; and (2) the applicant admits that ucf-101 could substantially inhibit its ability to induce caspase-independent apoptosis (see the specification page 19, lines 11-13), which means that there is a

possibility that just because ucf-101 showed profound effect on the activity of Omi/HtrA2 does not guarantee that it would inhibit caspase-independent apoptosis. The applicant's later prove that ucf-101 inhibit caspase-independent apoptosis (see page 46, paragraph 2, lines 14-16) but not any apoptosis inhibiting compound or the compounds shown in Fig. 1a, 2a, 2b, 3a, 3b, 4a, and 4b. Genetech, 108 F. 3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable.

In conclusion, the applicant is enabled for inhibiting caspase-independent apoptosis in a cell comprising contacting a cell having Omi/HtrA2 activity with the compound shown in Fig 1b (ucf-101), but not for any apoptosis inhibiting compound or the compounds shown in Fig. 1a, 2a, 2b, 3a, 3b, 4a, and 4b.

(2) Claims 20-22 and 28-29, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting Omi/HtrA2 activity comprising the compounds shown in Fig. 1a, 1b, 2a, 2b, 3a, 3b, 4a, and 4b, does not reasonably provide enablement for all apoptosis inhibiting compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to using the invention commensurate in scope with these claims.

The instant claims are drawn to a method of inhibiting Omi/HtrA2 activity with an apoptosis inhibiting compound. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the invention:

The claim 20 is drawn to " a method of inhibiting Omi/HtrA2 activity, comprising: contacting a cell having Omi/HtrA2 activity with an apoptosis inhibiting compound; and monitoring the inhibition of Omi/HtrA2 activity."

(2) The breadth of the claims:

Claims 20-22 embraces inhibiting Omi/HtrA2 activity, comprising: contacting a cell having Omi/HtrA2 activity with an apoptosis inhibiting compound. This reads on

inhibiting Omi/HtrA2 activity, with any apoptosis inhibiting compound. The specification does not enable inhibition of Omi/HtrA2 activity with any apoptosis inhibiting compound.

(3) The state of the prior art:

The state of the art regarding inhibition of Omi/HtrA2 activity with any apoptosis inhibiting compound is very low or do not exist.

(4) The predictability or unpredictability of the art:

The predictability of inhibiting Omi/HtrA2 activity with any apoptosis inhibiting compound is relatively low. Therefore, to one skilled in the art, inhibiting Omi/HtrA2 activity with any apoptosis inhibiting compound is highly unpredictable.

(5) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented / working examples:

In the instant case, the guidance of the specification as to the inhibition of Omi/HtrA2 activity with any apoptosis inhibiting compound is completely lacking. The specification as filed does not speak on or show any working examples any studies performed that inhibit Omi/HtrA2 activity with any apoptosis inhibiting compound. The specification does show on page 18 and 19 that the structure shown in Fig. 1a, 1b, 2a, 2b, 3a, 3b, 4a, and 4b had significant and specific activity against the protease in an *in*

vitro assay, with the highest activity exhibited by ucf-101 (Fig. 1b). Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2194.

(7) The quantity of experimentation necessary:

The instant claims read on the inhibition of Omi/HtrA2 activity with any apoptosis inhibiting compound. As discussed above the specification fails to provide any support for inhibiting Omi/HtrA2 activity with any apoptosis inhibiting compound. Applicant fails to provide any information sufficient to practice the claimed invention, absent undue experimentation. As stated above, the compounds with the structure shown in Fig. 1a, 1b, 2a, 2b, 3a, 3b, 4a, and 4b had significant and specific activity against the protease in an *in vitro* assay, with the highest activity exhibited by ucf-101 (Fig. 1b; see the specification page 19, lines 11-13). The applicant shows that several compound had weak activity against Omi and after two rounds of selection only one compound (ucf-101) showed substantial and reproducible inhibition against Omi (see page 37, lines 1-5, 9-12, and 22-25), thus proving that all apoptosis inhibiting compounds specifically and reproducibly inhibit Omi/HtrA2. Genetech, 108 F. 3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable.

In conclusion, the applicant is enabled for treating inhibiting Omi/HtrA2 activity comprising the compounds shown in Fig. 1a, 1b, 2a, 2b, 3a, 3b, 4a, and 4b, but not for inhibiting Omi/HtrA2 activity with any apoptosis inhibiting compound.

(3) Claims 30 and 31, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting caspase-independent apoptosis in a cell comprising the compound ucf-101 (i.e. Fig 1b; see specification page 45, example 15), does not reasonably provide enablement for modifying a disorder with caspase-independent apoptosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to using the invention commensurate in scope with these claims.

The instant claims are drawn to a method of modifying a disorder associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising at least one apoptosis inhibiting compound. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the invention:

The claim 30 is drawn to "a method for modifying a disorder associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising at least one apoptosis inhibiting compound such that the apoptosis inhibiting compound interacts with Omi/HtrA2 to inhibit the activity of Omi/HtrA2, wherein the inhibition of Omi/HtrA2 activity reduces apoptosis in the cell; and monitoring the amelioration of the disorder by measuring the change in caspase-independent apoptosis." The claim 31 is drawn to "a method of claim 30, wherein the disorder is selected from the group consisting of kidney failure, heart failure, heart attack, stroke, neurodegenerative disease, cancers and tumors.

(2) The breadth of the claims:

Claims 30 and 31 embraces modifying a disorder associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising at least one apoptosis inhibiting compound. This reads on treating all disorders, specifically kidney failure, heart failure, heart attack, stroke, neurodegenerative disease, cancers and tumors with any apoptosis inhibiting

compound. The specification does not enable modifying all disorders associated with caspase-independent apoptosis comprising at least one apoptosis inhibiting compound.

(3) The state of the prior art:

The state of the art regarding modifying all disorders associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising at least one apoptosis inhibiting compound is very low or do not exist.

(4) The predictability or unpredictability of the art:

The predictability of modifying all disorders associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising at least one apoptosis inhibiting compound is relatively low. Therefore, to one skilled in the art, modifying all disorders associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising at least one apoptosis inhibiting compound is highly unpredictable.

(5) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented / working examples:

In the instant case, the guidance of the specification as to modifying a disorder associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising at least one apoptosis inhibiting compound is completely lacking. The specification as filed does not speak on or show any working examples any studies performed that modify all or any disorder associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising at least one apoptosis inhibiting compound. The specification does mention that the invention can be used to prevent, reduce, or ameliorate disorders association with apoptosis and gives non-limiting examples of the disorders associated with apoptosis on page 26, section VIII. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2194.

(7) The quantity of experimentation necessary:

The instant claims read on modifying all and any disorder (specifically kidney failure, heart failure, heart attack, stroke, neurodegenerative disease, cancers and tumors) associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising at least one apoptosis inhibiting compound. As discussed above the specification fails to provide any support for modifying all and any disorder (specifically kidney failure, heart failure, heart attack, stroke, neurodegenerative disease, cancers and tumors) associated with caspase-independent apoptosis administering a therapeutically effective amount of a

composition comprising at least one apoptosis inhibiting compound. Applicant fails to provide any information sufficient to practice the claimed invention, absent undue experimentation. With no examples on that any apoptosis inhibiting compound or any of the applicant's compounds specifically treat or modify any disorder association with caspase-independent apoptosis, one skilled in the art does not know the following: (1) if the compound is effective; (2) what are all of the disorders to treat; or (3) how much to administer that would be therapeutic or effective. Genetech, 108 F. 3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" .and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable.

In conclusion, the applicant is enabled for inhibiting caspase-independent apoptosis in a cell comprising contacting a cell having Omi/HtrA2 activity with the compound shown in Fig 1b (ucf-101), but not for modifying all or any disorder (specifically kidney failure, heart failure, heart attack, stroke, neurodegenerative disease, cancers and tumors) associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising at least one apoptosis inhibiting compound.

(4) Claims 30 and 31, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting caspase-independent apoptosis in a cell comprising the compound ucf-101 (i.e. Fig 1b;

see specification page 45, example 15), does not reasonably provide enablement for modifying a disorder with caspase-independent apoptosis with <u>any</u> apoptosis inhibiting compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to using the invention commensurate in scope with these claims.

The instant claims are drawn to a method of modifying a disorder associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising at least one apoptosis inhibiting compound. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the invention:

The claim 30 is drawn to "a method for modifying a disorder associated with caspase-independent apoptosis administering a therapeutically effective amount of a

composition comprising at least one apoptosis inhibiting compound such that the apoptosis inhibiting compound interacts with Omi/HtrA2 to inhibit the activity of Omi/HtrA2, wherein the inhibition of Omi/HtrA2 activity reduces apoptosis in the cell; and monitoring the amelioration of the disorder by measuring the change in caspase-independent apoptosis." The claim 31 is drawn to "a method of claim 30, wherein the disorder is selected from the group consisting of kidney failure, heart failure, heart attack, stroke, neurodegenerative disease, cancers and tumors.

(2) The breadth of the claims:

Claims 30 and 31 embraces modifying a disorder associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising at least one apoptosis inhibiting compound. This reads on treating all disorders, specifically kidney failure, heart failure, heart attack, stroke, neurodegenerative disease, cancers and tumors with any apoptosis inhibiting compound. The specification does not enable modifying disorders associated with caspase-independent apoptosis comprising any apoptosis inhibiting compound.

(3) The state of the prior art:

The state of the art regarding modifying disorders associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising any apoptosis inhibiting compound is very low or do not exist.

(4) The predictability or unpredictability of the art:

The predictability of modifying all disorders associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising any apoptosis inhibiting compound is relatively low. Therefore, to one skilled in the art, modifying disorders associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising any apoptosis inhibiting compound is highly unpredictable.

(5) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented / working examples:

In the instant case, the guidance of the specification as to modifying a disorder associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising at least one apoptosis inhibiting compound is completely lacking. The specification as filed does not speak on or show any working examples any studies performed that modify disorders associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising any apoptosis inhibiting compound. The specification does mention that the invention can be used to prevent, reduce, or ameliorate disorders association with apoptosis and gives non-limiting examples of the disorders associated with apoptosis on page 26, section VIII. Note that lack of a working example, is a

critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2194.

(7) The quantity of experimentation necessary:

The instant claims read on modifying disorders (specifically kidney failure, heart failure, heart attack, stroke, neurodegenerative disease, cancers and tumors) associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising any apoptosis inhibiting compound. As discussed above the specification fails to provide any support for modifying disorders (specifically kidney failure, heart failure, heart attack, stroke, neurodegenerative disease, cancers and tumors) associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising any apoptosis inhibiting compound. Applicant fails to provide any information sufficient to practice the claimed invention, absent undue experimentation. With no examples on that any apoptosis inhibiting compound or any of the applicant's compounds specifically treat or modify any disorder association with caspase-independent apoptosis, one skilled in the art does not know the following: (1) if the compound is effective; (2) what are all of the disorders to treat; or (3) how much to administer that would be therapeutic or effective. Genetech, 108 F. 3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable.

In conclusion, the applicant is enabled for inhibiting caspase-independent apoptosis in a cell comprising contacting a cell having Omi/HtrA2 activity with the compound shown in Fig 1b (ucf-101), but not for modifying a disorder (specifically kidney failure, heart failure, heart attack, stroke, neurodegenerative disease, cancers and tumors) associated with caspase-independent apoptosis administering a therapeutically effective amount of a composition comprising at least one apoptosis inhibiting compound.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 12-14, 21-22, 28 and 29-31 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-8, 14, 15, and 18 of copending Application No. 10/369,311. This is a provisional obviousness-type double patenting rejection.

Although the conflicting claims 12-14, 21-22, 28 and 29-31 are not identical, they are not patentably distinct from each other because of the reasons below.

The application 10/369,311 ('311) teaches a method of inhibiting Omi/HtrA2 and cellular apoptosis (see claim 4) comprising reacting Omi/HtrA2 with a compound disclosed in claim 1 to a cellular solution (see claims 1 and 4). The cellular solution comprises eukaryotic and prokaryotic cells, including bacteria (i.e. *in vitro*; see claims 5-7). A method for treating a patient suffering from excessive cellular apoptosis comprising administering to said patient an inhibitor of Omi/HtrA2 (see claims 8) and a method for the treatment of a patient suffering from diseases whose etiology is rooted in excessive cellular apoptosis is also taught (i.e. *in vivo*; see claim 14). Diseases include stroke, Alzheimers and Parkinsons (see claim 15). Also taught is a method for screening compounds for the ability to inhibit Omi/HtrA2 comprising reacting a compound whose activity is to be tested with FITC-casein in the presence of MBP-$Omi_{134-458}$ and monitoring resulting changes in fluorescence (see claim 18).

The application '311 does not teach a method for inhibiting caspase-independent apoptosis (claim 12) or specifically monitoring apoptosis of the cell (claim 29).

To one of ordinary skill in the art at the time of the invention would have found it obvious to inhibit caspase-independent apoptosis because the target apoptosis protein is Omi/HtrA2 and not caspase. Additionally, the apoptosis of the cell is monitored because '311 teaches the ability to inhibit Omi/HtrA2 comprising reacting a compound whose activity is to be tested with FITC-casein in the presence of MBP-$Omi_{134-458}$ and monitoring resulting changes in fluorescence (see claim 18). Thus, since inhibiting Omi/HtrA2 results in apoptosis, then the limitation is met.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 12-14, 20-22, 28 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Alnemri (US 2003/0073629 A1).

Alnemri teaches the modulation of apoptosis, and more particularly to Omi/HtrA2 activation of apoptosis via a caspase-independent manner through its protease activity (see page 1, paragraph 3, lines 1-4; addresses claims 12 and 20) with a peptide (i.e. apoptosis inhibiting compound) that specifically binds to at least a portion of an inhibitor of apoptosis protein and serine protease (see abstract in its entirety and page 20, paragraph 191 lines 1-2; addresses claims 12 and 20). The compositions comprising the Omi peptide (i.e. apoptosis inhibiting compound) are used to inhibit apoptosis (see page 16, paragraph 157, lines 1-4) both in vitro and in vivo for the treatment of diseases such as cancer, neurodegenerative diseases and ischemic injury (see page 17, paragraph 171, lines 1-4, 6, and 10; addresses claims 12-14, 20-22, 30 and 31). The composition is administered in appropriate dosage amounts balancing toxicity and efficacy (see page 16, paragraph 161, lines 1-2; addresses claim 30)To determine if endogenous Omi plays a role in cell death, the percentages of GFP-positive apoptotic dells were determined by fluorescent microscopy (see page 20, lines 1-2 and 9-11; addresses claims 28-30).

Conclusion

Claims 12-14, 20-22, 28, and 29 are not allowed for the reasons given above. Although, claims 15-19 and 23-27 are free from the art and are considered allowable because the method comprises compounds not used in the art as apoptosis inhibiting

compounds, whereas the closest prior art (US 2005/0042213 A1) teaches the applicant's compounds (see claims142, 145, 155, and 156) as pro-heparanase binding agents.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kendra D. Carter whose telephone number is (571) 272-9034. The examiner can normally be reached on 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

KDC